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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Fleischer and Reimer

Confirmation No.: 8087

Serial No.: 09/701,220

Group Art Unit: 1615

Filed: November 27, 2000

Examiner: Gollamudi S. Kishore

For: PREPARATIONS FOR THE PROMOTION OF WOUND HEALING IN THE UPPER RESPIRATORY TRACT AND/OR EAR

Attorney Docket No.: 11390-004

PRE-APPEAL BRIEF CONFERENCE REQUEST

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Applicants hereby request review of the Final Rejection mailed May 11, 2006 ("Final Rejection") of the above-captioned application prior to filing an appeal brief for the reasons set forth below. Applicants submit that the Final Rejection fails to establish a *prima facie* rejection and that the evidence and arguments previously submitted by Applicants is nonetheless sufficient to overcome the Final Rejection in the event that the Examiner's rejection is found to be proper. A Notice of Appeal accompanied by the appropriate fee and a Petition for an Extension of Time for Response for two months from August 11, 2006 to October 11, 2006 accompanied by the appropriate fee are submitted herewith.

The present invention is generally related to using liposomes containing povidone iodine to suppress undesired tissue formation, *i.e.*, scar formation, or to restore the original appearance of the tissue at a site of tissue damage in the upper respiratory tract or ear. In particular, independent claim 54 is directed to a method for suppressing undesired tissue formation or for restoring the original appearance of tissue at a site of tissue damage in the upper respiratory tract or ear of a patient by administering to a patient in need thereof at the site of tissue damage, an amount of liposomes sufficient to suppress undesired tissue formation or to restore the original appearance of the tissue, said liposomes containing povidone iodine. Further, independent claim 77 is directed to a method for suppressing scar formation at a site of tissue damage in the upper respiratory tract or ear of a patient by administering to a patient in need thereof at the site of

tissue damage, an amount of liposomes sufficient to suppress scar formation, said liposomes containing povidone iodine. Further, independent claim 78 is directed to a method for suppressing undesired tissue formation or for restoring the original appearance of tissue at a site of tissue damage in the ciliary epithelial tissues in the upper respiratory tract or ear of a patient by administering to a patient in need thereof at the site of tissue damage, an amount of liposomes sufficient to suppress undesired tissue formation or to restore the original appearance of the tissue, said liposomes containing povidone iodine.

Applicants note that the tissue damage may be caused by an infection; however, the claims are not limited to damage caused by an infection. Applicants further note that the presently pending claims are not directed to treating infections. Applicants note that liposomes containing povidone iodine are sufficient in and of themselves to suppress undesired tissue formation or to restore the original appearance of a tissue or to suppress scar formation. No additional wound healing agents are required, although such agents may be optionally added.

The Examiner has maintained the rejection of independent claims 54, 77 and 78 and dependent claims 55-76 under 35 U.S.C. § 103(a) as allegedly obvious over European Patent No. 639373 ("the '373 patent") in view of U.S. Patent No. 5,049,388 to Knight *et al.* ("Knight"). Further, the Examiner has maintained a second rejection of the pending claims under 35 U.S.C. § 103(a) as allegedly obvious over the '373 patent in view of Knight further in view of International Patent Publication No. WO 85/00112 ("the '112 Publication"). The Examiner has stated that he has provided a clear and particular showing to combine the cited references. Applicants disagree and respectfully submit that not only is there no suggestion or motivation in the prior art to use iodine-containing compounds in wound healing, there is also no suggestion or motivation to administer iodine compounds to internal body tissues, including ciliated respiratory tract tissue. A rejection for obviousness is not supportable unless there is a suggestion in the art to combine the references and there is a reasonable expectation of success by one skilled in the art the invention can be achieved. As there is no suggestion to combine the teachings of the references and there is no expectation of success, the Examiner has not met his burden of presenting a *prima facie* case of obviousness.

The '373 patent teaches that liposomes containing povidone iodine can be administered externally, *i.e.*, to the skin or eye, for treatment of an infection. Further, the '373 patent teaches that when liposomes containing povidone iodine also contain a wound healing promoting agent, such liposomes can be used to treat an infection and to promote wound healing. According to the Declaration of Dr. Fleischer ("Declaration") submitted previously, a person of ordinary skill in the art, upon reading the '373 patent, would recognize that in order to promote the healing of

an external wound, liposomes containing a wound healing promoting agent need to be administered to the site of the wound. The '373 patent discloses on page 3, line 15 that such wound healing promoting agents include compounds such a vitamins, allantoin and some azulenes. Thus, the '373 patent teaches that promoting wound healing is not the result of the application of liposomes containing povidone iodine, but, rather, is the result of the application of liposomes containing povidone iodine further containing a wound healing promoting agent. There is no disclosure in the '373 patent that teaches or suggests that liposomes containing povidone iodine can be used without a wound healing promoting agent for promoting the healing of wounds.

Not only is there no teaching in the '373 patent that liposomes containing iodine without a wound healing promoting agent can be administered to promote wound healing, the prior art actually taught away from using iodine compounds in wound healing because it had been shown that iodine compounds interfered with wound healing. According to the Declaration at ¶ 7, Dr. Fleischer explained that it was well known prior to the filing of the present application that iodine and iodine-containing compounds such as povidone iodine are highly oxidizing agents that have been used as topical disinfectants and anti-infectants. Dr. Fleischer further explained that it was also well known in the art that iodine and iodine compounds can adversely effect wound healing. As evidence for his assertions, Dr. Fleischer referred to Lineaweaver *et al.*, 1985, Arch Surg 120:257-270, (disclosing that povidone iodine significantly retarded wound healing) and to Kallenberger *et al.*, 1991, Hyg + Med 16:383-395 (disclosing that application of antiseptics, such as the iodophores Braunol® and Betadine®, significantly reduced proliferation rates of epithelial cells). In view of the teachings of the prior art, Dr. Fleischer concluded that "a skilled artisan would not have been motivated to apply iodine compounds to external wounds in order to enhance wound healing."

Further, Applicants point out that there is no teaching or suggestion in the '373 patent that the liposomes containing povidone iodine could be administered to any other part of the body other than to external parts of the body, such as the skin and the mucous membrane of the eye. Upon reading the '373 patent in its entirety, *i.e.*, as a whole, it is clear that there is no teaching or suggestion to administer the liposomal formulation of povidone iodine and a wound healing promoting agent to an internal body part, including the upper respiratory tract and ear. The '373 Patent consistently teaches that the formulations are for external application, such as treatment of an eye infection or treatment of an external wound of the skin, not to internal areas of the body. Applicants note that the mucosa of the eye is not considered by those of skill in the art as an internal tissue.

Moreover, the prior art taught actually away from application of an antiseptic agent like povidone iodine to more sensitive internal tissue, especially respiratory tract tissue, due to the known harsh oxidizing nature of iodine and the knowledge that iodine can damage and/or kill cells. As Dr. Fleischer explained in ¶ 8 of the Declaration, much of the tissue in the upper and lower respiratory tract is lined with ciliated cells, which cells are required for proper lung function. The cilia on the lung cells move (beat) in unison (frequency around 16 Hz) to expel mucous and contaminants from the lungs. Where the cilia do not function properly, lung function is impaired and can lead to disease and death. Cystic fibrosis is one exemplary disease resulting from non-functioning cilia. Dr. Fleischer stated that "[i]n view of the importance of not harming ciliated cells and in view of the known ability of iodine compounds to damage cells, one skilled in the art would not have been motivated to apply iodine compounds to the respiratory tract for any reason for fear of damaging the ciliated cells." Declaration at ¶ 8. This *in vitro* assay is certainly indicative of the *in vivo* effects of the same compounds on ciliated respiratory tissue.

Knight does not fill in the gap between the claimed invention and the disclosure of the '373 patent. Knight discloses small aqueous aerosol droplets containing liposomes and wherein such liposomes are interacted with drugs, and their use in treating medical conditions in the lungs. No where does Knight teach, much less, suggest that such liposomes can be used for suppressing undesired tissue formation or for restoring the original appearance of tissue at a site of tissue damage in the respiratory tract. Moreover, Knight does not teach or suggest that the liposomes can be interacted with povidone iodine, which is an aggressive oxidizing antiseptic, not a drug such as an antibiotic. As set forth in ¶ 16 of the Declaration, Dr. Fleischer stated that he has reviewed the Knight reference and that Knight discloses that liposomes can be administered to the respiratory tract. Dr. Fleischer continued that it is his opinion that none of the compounds that are taught to be formulated with liposomes in Knight is in the same class of compounds as povidone iodine, which is a highly oxidative chemical antiseptic agent. Dr. Fleischer concluded that it is his belief that administration of the liposomal formulations of Knight is not suggestive of administration of liposomal formulations of povidone iodine to the upper respiratory tract and/or non-external parts of the ear because the compounds formulated with liposomes by Knight are not in the same class of compounds to which povidone iodine belongs.

There is nothing in the '373 patent or in Knight, alone or in combination, that teaches or suggests that liposomes containing povidone iodine alone can be used to suppress undesired tissue formation or for restoring the original appearance of tissue at a site of tissue damage in the

upper respiratory tract. Further, since the prior art teaches away the administration of iodine compounds for the purpose of wound healing, as well as teaches away the administration of iodine compounds to an interior part of the body for any reason, the Examiner has not provided the required reasonable expectation of success in achieving the claimed methods.

With regard to the Examiner's second Section 103 rejection citing the same references above in combination with the '112 Publication, Applicants submit that this reference also fails to fill in the gap between the claimed invention and the previously cited prior art. The '112 Publication teaches that microbiocidal agents, including povidone iodine, can be administered by inhalation of a stream or heated air containing the agents to the nasal passages. There is no disclosure of liposomes, nor is there any disclosure of suppressing undesired tissue formation at a site of tissue damage. As the pending claims are not directed to treating infections, Applicants fail to see how the '112 Publication is relevant to the presently pending claims other than to teach that povidone iodine can be administered to nasal passages for treating a cold. There is no teaching with regard to the applicability of povidone iodine to ciliated respiratory tissue or to the larynx or middle ear, much less for the purpose of preventing, *e.g.*, scar formation.

Thus, Applicants submit that the Examiner has not provided the required suggestion, teaching or motivation to combine the teachings of the '373 patent with the teachings of Knight or the '112 Publication. Thus, Applicants respectfully submit that these Section 103 rejections are in error and request that these rejections be withdrawn.

CONCLUSION

For at least the reasons above, Applicants submit that independent claims 54, 77 and 78 are in condition for allowance. As claims 55-76 depend from independent claim 54, Applicants submit that these claims are likewise in condition for allowance.

Respectfully submitted,

Date: September 20, 2006

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